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New pharmaceutical composition and the process for its preparation

FIELD OF THE INVENTION

The subject-matter of the present invention is a new pharmaceutical composition containing (-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid as active ingredient and the process for its preparation.

BACKGROUND OF THE INVENTION

(-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid and pharmaceutically acceptable salts thereof has been found useful in the treatment of type 2 diabetes acting as a insulin sensitizer as disclosed in PCT Publication WO 99/19313.

In WO 99/19313 the active ingredient is present as the base or as a pharmaceutically acceptable salt, preferably as the sodium salt.

SUMMARY OF THE INVENTION

The aim of the present invention is to provide a new compositions intended for the preparation of (-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or of one of its pharmaceutically acceptable salts with improved stability, in particular solid dosage forms thereof.

DESCRIPTION OF THE INVENTION

It has been found in fact that (-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid and its pharmaceutically acceptable salts may decompose in the presence of and in contact with water. Further it has been observed that decomposing may occur in the presence of oxygen.

Thus, from a first aspect, the subject-matter of the present invention is a pharmaceutical composition intended for the preparation of dosage forms and in particular solid dosage

forms containing an efficacious quantity of (-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or of one of its pharmaceutically acceptabl salts as active ingredient.

The present invention is based on the surprising discovery of the fact that the stability of (-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, or of one of its pharmaceutically acceptable salts, can be considerably improved in preparations containing (-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or of its pharmaceutically acceptable salts and antioxidant agent if the product is composed of excipients which do not contain water.

Another characteristic of the invention is, that a surprisingly very high degree of mixing homogeneity can be obtained with (-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid in low concentrations in powder and tablet formulations using a certain combination of pharmaceutical fillers, adjuvants and mixing process.

Pharmaceutically acceptable salts forming part of this invention include salts such as alkali metal salts like Li, Na, and K salts, alkaline earth metal salts like Ca and Mg salts, salts of organic bases such as lysine, arginine, guanidine, diethanolamine, choline and the like, ammonium or substituted ammonium salts, aluminium salts. Salts may include acid addition salts where appropriate which are, sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, succinates, palmoates, methanesulplionates, benzoates, salicylates, hydroxynaphthoates, benzenesulfonates, ascorbates, glycerophosphates, ketoglutarates and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 1977, 66, 2, which is incorporated herein by reference.

In a preferred embodiment (-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, arginine is used in the present invention.

(-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, together with a conventional adjuvant, antioxidant carrier, or diluent, and if desired a pharmaceutically acceptable acid addition salt thereof, may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or oral powders to b diluted imm diat ly befor use filled with th sam , all for oral use, in the form of suppositories for rectal administration; or as pessaries for vaginal

use; or in th form of sterile injectable powd rs for par nteral, transdermal, nasal, pulmonary and ocular use.

Within the framework of the present description and of the claims, by powders is meant any mixture of components, granulated or not, intended to be placed in solution and/or in suspension in water, or again to be ingested directly or by any other appropriate means as for example in a mixture with a food product.

In accordance with a particular characteristic of the invention, the manufacture of tablets are carried out as a direct compression.

In accordance with another particular characteristic, this composition also contains pharmaceutically acceptable excipients.

In accordance with a particular characteristic of the invention, the antioxidant agent cited above is selected from among α-tocopherol, γ-tocopherol, δ-tocopherol, extracts of natural origin rich in tocopherol, L-ascorbic acid and its sodium or calcium salts, ascorbyl palmitate, propyl gallate (PG), octyl gallate, dodecyl gallate, butylated hydroxy anisole (BHA) and butylated hydroxy toluene (BHT).

In accordance with a currently preferred embodiment, the antioxidant agent will be α-tocopherol.

In accordance with another particular characteristic of the invention, the diluent is lactose and/or cellulose microcrystalline, magnesium stearate, talc.

However, any other pharmaceutically acceptable diluents could be used if the diluents has a low water content.

The quantities of diluents can be easily determined by a person skilled in the art and depend of course on the final pharmaceutical form required.

Generally speaking, a composition which complies with the present invention and which are intended for the preparation of tablets, may contain, xpressed in parts by w ight per 100

parts of (-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]ph nyl]-2-ethoxypropanoic acid, or of on of its pharmaceutically acceptable salts:

between 100 and 400,000 parts by weight of anhydrous lactose;
between 100 and 400,000 parts by weight of lactose monohydrate
between 100 and 400,000 parts by weight of dibasic calciiumphosphate
between 1 and 100 parts by weight of an antioxidant;
between 50 and 500 parts by weight of pregelatinized starch;
between 1000 and 10,000 parts by weight of microcrystalline cellulose;
between 10 and 500 parts by weight of crospovidone;
between 10 and 500 parts by weight of silicon dioxide;
between 10 and 500 parts by weight of hydrogenated vegetable oil;
between 10 and 500 parts by weight of magnesium stearate;
between 10 and 500 parts by weight of hydroxypropyl methylcellulose;
between 10 and 500 parts by weight of hydroxypropyl cellulose;
between 1000 and 10,000 parts by weight of Mannitol;
between 10 and 500 parts by weight of stearic acid;
between 10 and 500 parts by weight of Titanium Dioxide;

According to a preferred embodiment of the invention the water content of the excipients is very low. More specifically the water content in the diluents is very low in order to minimize the water content of the pharmaceutical composition. Lactose is used in its anhydrous form.

Furthermore, all excipients may be applied in a dry form.

In accordance with a second aspect, the subject-matter of the present invention is a pharmaceutical preparation, in the form of tablet or powder, characterised in that it contains a composition as defined previously associated if required with at least one customary additive selected from among the sweeteners, flavouring agents, colours and lubricants.

Another manufacturing process for pharmaceutical compositions according to the invention is mixing of (-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, one or more antioxidants and other pharmaceutical xcipi nts followed by melt granulation in a high shear mixer. Hydrog nat d, vegetable oil, waxes or other low temperature melting bind rs

can be used. The granul s can be filled into capsules, compressed into tablets or used in other pharmac utical dosage forms.

More preferably the manufacturing process applied is direct compression of tablets, wherein (-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, one or more antioxidants and other excipients suitable for direct compression are mixed followed by tabletting.

Yet, another preferred embodiment of the manufacturing process is wet granulation, where granules are obtained by wet massing of (-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, together with one or more antioxidants and other excipients.
It is assumed that the contact time with water has to be very short.

The most preferred process comprises the direct compression whereby (-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid is kept at conditions of low water vapour pressure.

A sweetener may be a natural sugar such as sorbitol or a synthetic product such as saccharine or aspartame.

When the antioxidant selected is ascorbylpalmitat, propylgallat, which is a powder, it can be advantageous to mix it in an appropriate excipient such as α-tocopherol succinat, lactose or cellulose micrycrystalline.

The present invention will further be illustrated with the following non-exhaustive examples.

EXAMPLES

In Example 1 through 5 the tablets were prepared according to the following procedure:

The active ingredient is mixed with cellulose microcrystalline by hand
Lactose is added and the mixing continues in an drum mixer for 5 minutes.
The talc is added and the mixing continues for 2 minutes.
The magnesium stearate is added and the mixing continues for 1 minute more.

EXAMPLE 1

(-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid 0.5 mg

(-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid ,arginine 0.353%

Cellulose Microcrystallline	20%
Lactose	75%
Magnesium Stearate	0.5%
Talc	4.5%

EXAMPLE 2

(-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid 10 mg

(-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid,arginine 7.075%

Cellulose Microcrystalline	20%
Lactose	67.95%
Magnesium Stearate	0.5%
Talc	4.5%

EXAMPLE 3

(-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl-2-ethoxypropanoic acid, 0.1 mg with a total mass of 80 mg

(-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl-2-ethoxypropanoic acid, arginine 0.18%

Tablettose 80	96.12%
Avicel PH 102	3.00%
Cab-Osil M-3	0.20%
Magnesium Stearate	0.50%

At higher strengths the amount of (-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl-2-ethoxypropanoic acid arginine will be subtracted from Tablettose 80.

Manufacturing procedur :

The active ingr di nt is sieved through a 0.125 to 0.4 mm sieve and mixed with the sam amount of Tablettose 80. Cab-Osil is sieved through a 1.0 mm sieve together with a small amount of Tablettose. The active ingredient, Tablettose, Avicel and Cab-Osil are mixed in a drum mixer in the range of 20 to 30 minutes depending on the strengths manufactured. Magnesium Stearate is sieved through a 0.125 mm sieve immediately before use and is mixed with the other ingredients in a drum mixer for 3 more minutes.

EXAMPLE 4

(-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl-2-ethoxypropanoic acid, 0.5 mg

(-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl-2-ethoxypropanoic acid, arginine	0.353%
Lactose	87.65 %
Polyethylenglycol 6000	7 %
Talc	5 %

The granulate is manufactured in a Diosna 1 L high-shear mixer - using a water bath of 70°C. The mixing is carried out at 2000 RPM, chopper 1600 RPM and the granulation is performed at approx. 70°C. The hot granulate is sieved through sieve 1.00mm, and the cold granulate through sieve 1000mm . The glidant is added with a card for 2 min. The tablets are manufactured using a Korsch tabletmachine with ovale punch.

EXAMPLE 5

(-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl-2-ethoxypropanoic acid, 10 mg

(-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl-2-ethoxypropanoic acid, arginine	7.075%
Lactose	80.95%
Polyethylenglycol 6000	7 %
Talc	5 %

The granulate is manufactured in a Diosna 1 L high-shear mixer - using a water bath of 70°C. The mixing is carri d out at 2000 RPM, chopper 1600 RPM and the granulation is per-

formed at approx. 70°C. Th hot granulate is sieved through si v 1.00mm, and the cold granulate through si v 1000mm . The glidant is added with a card for 2 min. Th tablets are manufactured using a Korsch tabletmachine with ovale punch.

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CLAIMS

1. Pharmaceutical composition comprising
(-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or a pharmaceutically acceptable salt thereof,
and optionally a pharmaceutically acceptable carrier.

2. A composition according to claim 1 in the form of a tablet, a powder or a capsule.

3. A process for the preparation of a composition according to claim 1 or 2 which comprises the step of forming a mixture of:
(-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or a pharmaceutically acceptable salt thereof,
and one or more pharmaceutically acceptable carriers.

4. A process for the preparation of a composition according to claim 1 or 2 which comprises the following steps:
forming a mixture according to claim 3,
and direct compression of the mixture with excipients of a low water content.

5. A process according to claim 3 or 4 characterized in that the steps are carried out at low water vapour pressure and low oxygen pressure.

6. A pharmaceutical composition comprising
(-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or a pharmaceutically acceptable salt thereof,
and pharmaceutically acceptable excipients with low water content and an antioxidant.

7. The pharmaceutical composition according to claim 6 in the form of a tablet, a powder or a capsule.

8. The pharmaceutical composition according to claim 6 or 7 containing, expressed in parts by weight per 100 parts of (-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, or of one of its pharmaceutically acceptabl salts and betw n 1 and 100 parts by

weight of an antioxidant and the pharmaceutically acceptable xcipients s l cted among th following:

betwe n 100 and 400,000 parts by weight of anhydrous lactos ,

between 100 and 400,000 parts by weight of lactose monohydrate

between 100 and 400,000 parts by weight of dibasic calciiumphosphate

between 50 and 500 parts by weight of pregelatinized starch,

between 1000 and 10,000 parts by weight of microcrystalline cellulose,

between 10 and 500 parts by weight of crospovidone,

between 10 and 500 parts by weight of silicon dioxide,

between 10 and 500 parts by weight of hydrogenated vegetable oil,

between 10 and 500 parts by weight of magnesium stearate,

between 10 and 500 parts by weight of hydroxypropyl methylcellulose,

between 10 and 500 parts by weight of hydroxypropyl cellulose,

between 1000 and 10,000 parts by weight of Mannitol,

between 10 and 500 parts by weight of stearic acid,

between 10 and 500 parts by weight of Titanium Dioxide.

9. The pharmaceutical composition according to claim 6 or 7 wherein the pharmaceutically acceptable excipients are selected among from the following:

between 100 and 400,000 parts by weight of anhydrous lactose,

between 100 and 400,000 parts by weight of lactose monohydrate

between 100 and 400,000 parts by weight of dibasic calciiumphosphate

between 50 and 500 parts by weight of pregelatinized starch,

between 1000 and 10,000 parts by weight of microcrystalline cellulose,

between 10 and 500 parts by weight of crospovidone,

between 10 and 500 parts by weight of silicon dioxide,

between 10 and 500 parts by weight of hydrogenated vegetable oil,

between 10 and 500 parts by weight of magnesium stearate,

between 10 and 500 parts by weight of hydroxypropyl methylcellulose,

between 10 and 500 parts by weight of hydroxypropyl cellulose,

between 1000 and 10,000 parts by weight of Mannitol,

between 10 and 500 parts by weight of stearic acid,

between 10 and 500 parts by weight of Titanium Dioxide,

expressed in parts by weight per 100 parts of (-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, or of one of its pharmaceutically acceptable salts.

10. The pharmaceutical composition according to claim 6 or 7 wherein the pharmaceutically acceptable excipients are selected from the following:
lactose and/or cellulose microcrystalline, magnesium stearate or talc.

11. The pharmaceutical composition according to claim 6 or 7 wherein the pharmaceutically acceptable excipients have a low water content.

12. The pharmaceutical composition according to claim 6 or 7 wherein the pharmaceutically acceptable excipients have a very low water content.

13. The pharmaceutical composition according to claim 6 or 7 wherein the pharmaceutically acceptable excipients are in a dry form.

14. The pharmaceutical composition according to claim 6 or 7 wherein the antioxidant is selected from the following:
α-tocopherol, γ-tocopherol, δ-tocopherol, extracts of natural origin rich in tocopherol, L-ascorbic acid and its sodium or calcium salts, ascorbyl palmitate, propyl gallate (PG), octyl gallate, dodecyl gallate, butylated hydroxy anisole (BHA) or butylated hydroxy toluene (BHT).

15. The pharmaceutical composition according to claim 6 or 7 wherein the antioxidant is α-tocopherol.

16. The pharmaceutical composition according to claim 1,2, 6 or 7 associated with at least one customary additive selected from among the sweeteners, flavouring agents, colours and lubricants.

17. A process for the preparation of a composition according to claim 6 or 7 which comprises the step of forming a mixture of:
(-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or a pharmaceutically acceptable salt thereof,
and one or more pharmaceutically acceptable excipients and an antioxidant.

18. A process for the preparation of a composition according to claim 6 or 7 which comprises the following steps:

forming a mixture according to claim 17, and direct compression of the mixture.

19. A process according to claim 17 or 18 charact rized in that the steps are carried out at low water vapour pressure and low oxygen pressure.

20. The pharmaceutical composition according to anyone of the preceding claims comprising the following:

(-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, arginine 0.353%

Cellulose Microcrystallline	20%
Lactose	75%
Magnesium Stearate	0.5%
Talc	4.5%

21. The pharmaceutical composition according to anyone of the preceding claims comprising the following:

(-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, arginine 7.075%

Cellulose Microcrystalline	20%
Mannitol	6.95%
Magnesium Stearate	0.5%
Talc	4.5%

22. The pharmaceutical composition according to anyone of the preceding claims comprising the following:

(-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, arginine 0.18%

Tablettose 80	96.12%
Avicel PH 102	3.00%
Cab-Osil M-3	0.20%
Magnesium Stearate	0.50%

23. The pharmaceutical composition according to anyone of the preceding claims comprising the following:

(-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl-2-ethoxypropanoic acid, arginine 0.353%

Lactose	87.65 %
Polyethylenglycol 6000	7 %
Talc	5 %

24. The pharmaceutical composition according to anyone of the preceding claims comprising the following:

(-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl-2-ethoxypropanoic acid, arginine 7.075%

Lactose	80.95%
Polyethylenglycol 6000	7 %
Talc	5 %

25. A pharmaceutical composition according to anyone of the preceding claims wherein (-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, arginine is used.

ABSTRACT

The present invention provides a new stable pharmaceutical composition containing (-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid as active ingredient.